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Outcomes of persons with blastomycosis involving the central nervous system

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ABSTRACT

Blastomyces dermatitidis is a dimorphic fungus which is potentially life-threatening if central nervous system (CNS) dissemination occurs. Sixteen patients with proven or probable CNS blastomycosis are presented. Median duration of symptoms was 90 days; headache and focal neurologic deficit were the most common presenting symptoms. Magnetic resonance imaging (MRI) consistently demonstrated an abnormality, compared to 58% of computed tomography scans. Tissue culture yielded the pathogen in 71% of histology-confirmed cases. All patients who completed treatment of an amphotericin B formulation and extended azole-based therapy did not relapse. Initial nonspecific symptoms lead to delayed diagnosis of CNS blastomycosis. A high index of suspicion is necessary if there is history of contact with an area where *B. dermatitidis* is endemic. Diagnostic tests should include MRI followed by biopsy for tissue culture and pathology. Optimal treatment utilizes a lipid-based amphotericin B preparation with an extended course of voriconazole.

1. Introduction

The thermally dimorphic fungus *Blastomyces dermatitidis*, which exists in the soil of moist wooded areas (Bakerspigel et al., 1986; Denton et al., 1961), can cause blastomycosis, a local or systemic infection in humans and animals. Primary infection almost always occurs via inhalation of aerosolized conidia released from disrupted soil (Saccente & Woods, 2010) but may rarely result from direct soft tissue inoculation through a break in the skin. *B. dermatitidis* is endemic to parts of the United States and Canada, including the Canadian province of Manitoba and the Kenora region of Ontario where the incidence rates are 0.62 and 7.1 cases per 100,000, respectively (Crampton et al., 2002). Both regions fall within the catchment area of 2 tertiary care hospitals in Winnipeg, Manitoba.

Pulmonary blastomycosis is the most common form of the infection. Subclinical pulmonary blastomycosis has been reported in 30% of at-risk forestry workers in areas where *B. dermatitidis* is endemic (Vaaler et al., 1990). If the host response is inadequate to control the initial infection, *B. dermatitidis* can disseminate via the lymphohematogenous route, the most frequent sites being skin, bone, and genitourinary tract (Saccente & Woods, 2010). Among persons diagnosed with extra-pulmonary blastomycosis, involvement of the central nervous system (CNS) is estimated in 5–10% (Gonyea, 1978; Saccente & Woods, 2010), and in up to 33% of cases in an older autopsy series (Fetter et al., 1967).

The diagnosis of pulmonary and extra-pulmonary blastomycosis can be made rapidly on histopathologic examination, but microbiologic cultures are considered the gold standard (Patel et al., 2010). Blastomycosis of the CNS may present with leptomeningitis, encephalitis, or as solitary or multiple brain or spinal cord abscesses (Bariola et al., 2010; Wylen & Nanda, 1999). *B. dermatitidis* on routine hematoxylin and eosin stain (H&E) is a double-walled, broad-based budding yeast in a granulomatous host-reaction with or without micro-abscess formation and central necrosis. Silver impregnation such as Grocott's methenamine silver (GMS) can increase screening sensitivity while periodic acid-Schiff (PAS), in situ hybridization, and other histochemical stains can help differentiate *B. dermatitidis* from other fungi (Mukhopadhyay & Gal, 2010). Electron microscopy reveals nuclear material in viable yeast and shows cytoplasmic retraction in degenerate forms (Guccion et al., 1996; Jay et al., 1991).

To date, fewer than 125 cases of CNS blastomycosis have been reported, the majority representing single case reports or small series or published before the modern era of extended-spectrum azole therapy and MRI CNS imaging. Cases reported prior to 1965 have been previously summarized (Fetter et al., 1967). More recently described are 27 CNS biopsy specimens, 3 ventricular cytology specimens, 3 CNS autopsy specimens, 8 cerebrospinal fluid (CSF) cultures, and 19

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probable CNS blastomycosis cases based on proven *B. dermatitidis* in an extra-CNS site (Bakleh et al., 2005; Borgia et al., 2006; Chander et al., 2007; Chowfin et al., 2000; Cook, 2001; Cooper et al., 1988; Friedman et al., 2000; Gershan et al., 1994; Gonyea, 1978; Harley et al., 1994; Kravitz et al., 1981; Mangham et al., 1983; Mohazab et al., 1997; Panicker et al., 2006; Raftopoulos et al., 1986; Szeder et al., 2007; Taillan et al., 1992; Ward et al., 1995; Wu et al., 2005; Wylen & Nanda, 1999). A case series of 22 patients presenting to 6 different tertiary care centers in the United States has also recently been reported (Bariola et al., 2010). Two separate guidelines published within the past 5 years have addressed the management of CNS blastomycosis (Chapman et al., 2008; Limper et al., 2011). The body of literature supporting current recommendations, however, remains limited.

The aim of this study is to correlate clinical manifestations, diagnostic techniques (imaging, microbiology, histopathology), and therapy of CNS blastomycosis. We present the largest series of patients with proven or probable CNS blastomycosis evaluated by a single infectious disease referral service.

2. Methods

2.1. Data collection

The study was approved by the Research Ethics Board, Faculty of Medicine, University of Manitoba. We identified and reviewed medical records of patients diagnosed with blastomycosis, with clinical or radiographic evidence of CNS involvement who received care at the Health Sciences Centre or Saint Boniface General Hospital, Winnipeg, Manitoba, from January 1988 through November 2011. These 2 facilities are Manitoba's tertiary care hospitals. Cases of CNS blastomycosis were found by searching the medical records database of the 2 hospitals using the *ICD-9* code of 116.0 and *ICD-10* code of B40.9. The pathology and microbiology department databases were also searched. A standardized medical record review included demographics, past medical history, history of presenting illness, laboratory and pathology reports, imaging reports, treatment, and clinical outcomes.

We defined CNS blastomycosis as "proven" or "probable" based on previously described criteria (De Pauw et al., 2008) as follows. A "proven" diagnosis requires: a) compatible clinical or radiographic findings, and b) culture or histopathologic demonstration of *B. dermatitidis* obtained from cerebrospinal fluid (CSF) or CNS tissue. "Probable" CNS blastomycosis requires compatible clinical and radiographic findings in conjunction with proven non-CNS blastomycosis (culture or histopathology).

2.2. Microbiology analysis

Fungal CSF cultures were incubated for four weeks at 30 °C using Sabhi agar. Fungal tissue cultures were plated to Sabhi, inhibitory mold agar, and brain heart infusion with sheep blood agar and incubated at 30 °C for 4 weeks.

2.3. Histopathology analysis

Pathology specimens were reviewed by two experienced neuropathologists (MDB, SK). The features evaluated were site of specimen, density of fungal forms, intra- or extracellular location of fungal forms, wall thickness and type of budding, yeast diameter, and inflammatory response. Histochemical staining with GMS, periodic acid–Schiff (PAS), PAS-Alcian blue (PAS-Ab), and Congo red was used in addition to standard H&E. Inflammation was characterized with immunohistochemistry markers including CDs 3, 4, 8, 45, 68, and HLA-DR. Tissue was fixed in 2.5% glutaraldehyde followed by 1% osmium tetroxide for electron microscopy studies.

3. Results

3.1. Clinical

Sixteen patients with probable or proven CNS blastomycosis were evaluated (Table 1), with the majority of cases diagnosed after the year 2000, and one case each diagnosed in 1988, 1994, and 1997. Nine cases (56%) were proven by culture and/or direct histopathologic

Table 1
Summary of clinical manifestations.

Patient #	Age (years), sex	Year of diagnosis	Comorbidities	Presenting symptoms	Symptom duration (days)	Localization of CNS disease	CNS diagnosis	Other organ involvement	Other relevant diagnostics
1	13, F	2001	None	Back pain, FND	30	T12-L1	Proven	Pulmonary	Sputum +
2	37, M	2006	None	H/A, blurred vision, nausea, vomiting	60	Meninges	Proven	Pulmonary	BAL -
3	68, M	2005	DM	H/A, FND	90	Cerebellar parenchyma	Proven	Pulmonary	BAL +
4	37, M	1988	None	H/A, FND	105	Cerebellum	Probable	Bone and joint	Skin nodule Bx pathology +
5	37, M	2005	None	H/A, fever and chills	115	Epidural extension from skull	Proven	Pulmonary, skin, bone	Scalp Bx culture +
6	16, M	2004	None	H/A, FND, seizure	90	Cerebrum	Proven	Pulmonary	None
7	3, M	2001	None	Scalp lesion	60	Epidural extension from skull	Probable	Bone, skin	Scalp Bx pathology +
8	9, M	2006	None	H/A, fever and chills	150	Epidural space and meninges	Probable	Bone, skin	Scalp Bx pathology and culture +
9	59, M	1997	None	FND	28	Meninges	Probable	Pulmonary	None
10	57, M	1994	MPD	Altered mental status	180	Cerebrum and cerebellum	Probable	Pulmonary	BAL +
11	12, M	2005	None	H/A, fever and chills	21	Epidural space and cerebrum	Proven	Scalp	Scalp aspirate culture +
12	63, M	2002	ESRD	Seizure, FND	90	Cerebrum	Proven	Pulmonary, skin, bone	None
13	52, M	2002	DM	H/A, FND, partial seizure	60	Meninges and cerebellum	Proven	None	None
14	12, M	2005	None	H/A, Fever, hypopituitarism, FND	168	Meninges and pituitary stalk	Proven	None	Serum antibody +
15	3, M	2006	None	FND, fever	210	Cerebrum	Probable	None	Serum antibody +
16	63, M	2010	None	H/A, FND	900	Meninges and cerebrum	Probable	Pulmonary	None

Patients are numbered and correspond across Tables 1–5.
BAL = Bronchoalveolar lavage, Bx = Biopsy, DM = Diabetes mellitus, ESRD = End-stage renal disease, FND = Focal neurologic deficit, H/A = Headache, MPD = Myeloproliferative disorder (Polycythemia rubra vera).